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McCune-Albright Syndrome: How Many Endocrinopathies Can One Patient Have?

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FULLER ALBRIGHT could not have known the full extent of the endocrinopathies that eventually would come to be identified in association with the syndrome he described in 1937.[1] He delineated the triad of polyostotic fibrous dysplasia, cutaneous pigmentation, and precocious puberty after having encountered several such patients, starting in the early 1930s. Donovan McCune's original patient showed not only this classic triad but also hyperthyroidism.[2] Other endocrinopathies subsequently described in association with the McCune-Albright syndrome include acromegaly,[3] hyperprolactinemia,[4] hyperparathyroidism,[5] gynecomastia,[6] Cushing's syndrome,[7] breast cancer, gonadotropinomas, and hypophosphatemic rickets.[8]

Sexual precosity in this syndrome is more accurately termed "pseudoprecocious puberty," since it is generally accepted that it is not mediated via maturation of the hypothalamic-pituitary-ovarian axis. Many of these patients have been found to have autonomously functioning follicular cysts.[9] Thus, girls with sexual precosity have elevated estrogens without pubertal gonadotropins.[10] More than half of the female subjects with McCune-Albright syndrome have sexual precosity, some as early as the first month of life. Ovarian function in these patients is resistant to manipulation with luteinizing hormone releasing hormone, further confirming the autonomous nature of their ovarian function.[11] Sexual precosity is also described in male subjects.[12]

The second most common associated endocrinopathy is hyperthyroidism, which is believed to be due primarily to multinodular toxic goiter.[13] Cushing's syndrome, acromegaly, and hyperparathyroidism in association with McCune-Albright syndrome are likewise thought to be due to autonomously functioning nodular disease.

The most widely accepted hypothesis of the pathophysiology of the disorder has been that multiple, discrete areas of autonomously functioning cells arise in various tissues that harbor embryologically dysfunctional clones of cells.[14] This is compatible with the hypothesis that the disease is manifested only in mosaics.[15] Currently, defective signal transduction for glycoprotein hormones is thought to be the central feature of the disorder. It is thought that the G-protein may be "turned on" chronically. Other hypotheses hold that there is hypothalamic hyperfunction or that there is end-organ hypersensitivity to normal stimuli.

We describe a patient who is unique not in terms of the specific endocrine organs involved, but in the number of various endocrinopathies simultaneously occurring in the same patient.

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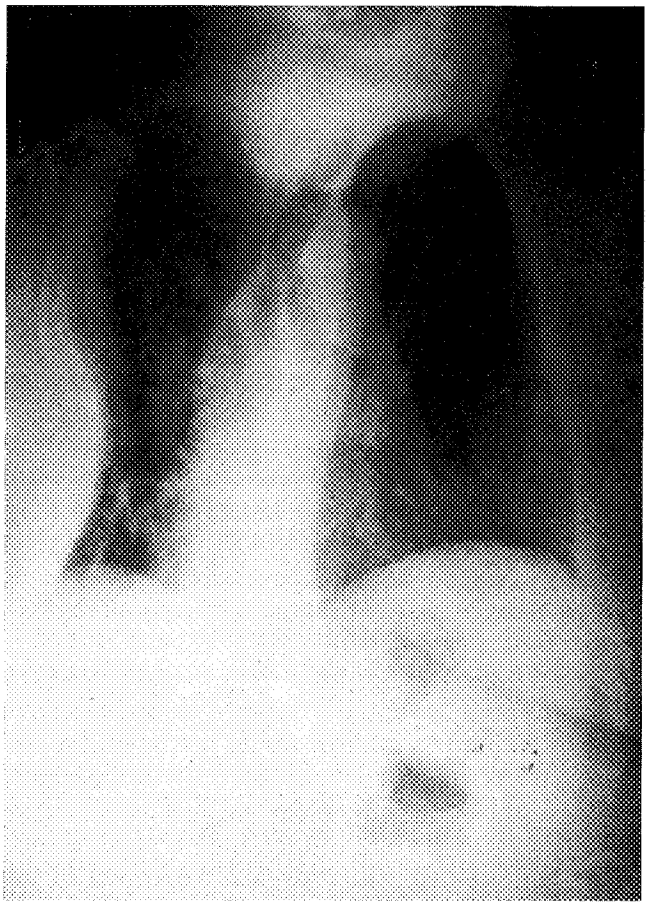

Bony lesions of fibrous dysplasia, diffuse osteopenia, and chest deformity.

TABLE 1. Laboratory Test Results

Laboratory Test	*Result*	*Normal Range*
Thyroxine	212 nmol/L	52.9 to 144.5
Triiodothyronine (T_3)	5.02 nmol/L	1.23 to 3.08
T_3 resin uptake	36%	25 to 35
Free thyroxine index	254 nmol/L	52.9 to 144.5
Thyroid hormone binding ratio	1.20	0.85 to 1.15
Sensitive thyrotropin	<0.05 mIU/L	0.40 to 4.60
Thyroglobulin	130 μg/L	0 to 60
Antithyroglobulin antibody	Negative	Negative
Antimicrosomal antibody	Negative	Negative
Somatomedin C	69 μg/L	64 to 163
Growth hormone	0.7 μg/L	0 to 20
Prolactin	3459 pmol/L	<888
Cortisol (AM)	0.50 μmol/L	0.20 to 0.76
Luteinizing hormone	6.7 IU/L	0 to 10
Follicle-stimulating hormone	3 IU/L	0 to 7
Estradiol	184 pmol/L	0 to 257
25-Hydroxy vitamin D	41 nmol/L	34 to 98
Intact parathyroid hormone	8.9 pmol/L	1.1 to 6.8
Total calcium	2.8 mmol/L	2.0 to 2.7
Ionized calcium	1.42 mmol/L	1.12 to 1.30
Phosphate	0.68 mmol/L	0.81 to 1.62
Alkaline phosphatase	278 IU/L	34 to 126
Albumin	33 g/dL	30 to 46
Magnesium	1.00 mmol/L	0.65 to 1.05
Sodium	141 mmol/L	135 to 150
Potassium	4.4 mmol/L	3.5 to 5.3
Chloride	102 mmol/L	95 to 110
Carbon dioxide	31 mmol/L	22 to 32
Urea nitrogen	3.9 mmol/L	1.8 to 7.9
Creatinine	44 μmol/L	62 to 133
Urinary calcium	4.2 mmol/day	2.5 to 7.5
Urinary phosphorus	18 mmol/day	10 to 45
Urinary creatinine	9.2 mmol/day	5.3 to 14.1
Urinary hydroxyproline	0.23 mmol/day	0.15 to 0.30

CASE REPORT

The patient is a 53-year-old white woman with the diagnosis of polyostotic fibrous dysplasia since age 9, when she had pathologic fractures of the femur, hip, and pelvis. At age 19 she had a pathologic fracture of the left humerus, and subsequently had numerous rib and hand fractures due to minimal, if any, trauma. Progressive kyphoscoliosis over many years resulted in loss of height. It was noted that she had generalized bone pain, though there was no evidence of any acute fractures. She had never received irradiation to any of the fibrous dysplasia lesions. She had no hearing loss, but did have a strabismus, which can occur with fibrous dysplasia involving the facial bones. She was given estrogens and calcium supplements for osteopenia in 1989, but she stopped taking them within a few weeks because of side effects.

Her gynecologic history was significant for menarche at age 9 (>2.5 standard deviations below the mean age of 13.2 years in the 1930s), a right salpingo-oophorectomy at age 26 for a "cyst," and early menopause at age 38. Her seven pregnancies comprised five miscarriages and two term deliveries via cesarean section.

She had a long history of worsening dyspnea on exertion, shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, and pedal edema dating from the mid 1980s and culminating in an admission to a civilian medical center with frank congestive heart failure and pneumonia in November 1990. She was noted to have severe restrictive lung disease, presumed to be due to extensive thoracic fibrous dysplasia with associated deformity. The congestive heart failure was attributed to chronic hypoxia from the restrictive lung disease. She was discharged with home oxygen therapy via nasal catheter at 1.5 L/min, as well as furosemide, potassium, digoxin, and an albuterol inhaler.

We were asked to see the patient in February 1991 for hyperthyroidism. She had a long history of heat intolerance, palpitations, nervousness, tremors, and weakness. She also had elevated thyroxin levels dating from at least as far back as 1989.

There was no family history of endocrinopathies or similar bone disease.

Physical examination revealed an obese, short female in moderate distress due to shortness of breath and skeletal pain. Her height was 137 cm, weight 72.3 kg, pulse rate 107/min, blood pressure 149/67 mm Hg, and respiratory rate 20/min. There was no stare, lid lag, or proptosis, but exotropia was present on the left. There were no facial features of acromegaly or Cushing's syndrome. Her lips were cyanotic. Neck examination (which was compromised by a short neck and obesity) revealed a 1 cm right-sided thyroid nodule without obvious goiter. Pulmonary examination revealed basilar rales, wheezes, and poor diaphragmatic excursion. A grade 2/6 systolic ejection murmur was noted across the precordium. No galactorrhea was noted. An 11 cm, lightly pigmented, irregular macular lesion was found on the left lower aspect of the back and a similar, smaller lesion on the right posterior part of the neck. As is characteristic of the syndrome, neither of

TABLE 2. Results of Procedures

Procedure	*Results*
Iodine I 123 thyroid scan	Heterogenous uptake, right greater than left, and 24-hour uptake of 55%
Thyroid ultrasonography	Right-sided thyroid cyst with focal mural calcification and attenuated left lobe
Dual energy x-ray absorptiometry	Decreased bone mineral density (74% of predicted)
Chest roentgenography	Extensive rib lesions consistent with fibrous dysplasia, kyphoscoliosis, osteopenia, compression fractures, chronic pulmonary scarring, vascular congestion, and loss of airspace
Pulmonary function testing	Total lung capacity, 1.5 L: forced vital capacity, 0.52 L (24% of predicted); forced expiratory volume during the first second 0.45 L (29% of predicted)
Arterial blood gas values (on room air)	pH 7.40, P_{O_2} 56 mm Hg, P_{CO_2} 59 mm Hg
Electrocardiogram	Sinus tachycardia
Echocardiogram	Normal left ventricular function without chamber enlargement
Magnetic resonance imaging of the pituitary	Patient unable to tolerate

the skin lesions crossed the midline. Also noted were white, nondepressed striae measuring less than 1 cm in width. No ecchymoses were noted. Examination of the extremities showed a fine tremor, pretibial edema, and moist palms.

Pertinent laboratory values are shown in Table 1. The 24-hour urine collection must be interpreted in the context of a patient receiving large doses of furosemide for long-term treatment of congestive heart failure. Results of a number of procedures are shown in Table 2.

DISCUSSION

The diagnosis of McCune-Albright syndrome was made. The bone disease was considered multifactorial in view of the patient's primary hyperparathyroidism, hyperthyroidism, premature menopause with hypoestrogenemia, and underlying polyostotic fibrous dysplasia (Figure).

The patient's early menopause put her at increased risk for osteoporosis. It is possible that the early cessation of menses was related to hyperprolactinemia and/or hyperthyroidism, though there is no proof that these endocrinopathies were present when the patient stopped menstruating at age 38.

The patient's short stature is of interest because patients with McCune-Albright syndrome generally achieve normal adult height unless they have rickets or puberty at an extremely young age. Our patient was never taller than 149 cm even before she lost height, and she has diffuse bone pain without evidence of recent fractures or 25-hydroxy vitamin D deficiency, which raises the possibility of hypophosphatemic rickets. Short stature in hypophosphatemic rickets, however, is thought to be due to bowing of lower extremities, which our patient did not appear to have. In addition, the diagnosis of primary hyperparathyroidism in this patient makes it impossible to make a case for hypophosphatemic rickets based on bony abnormalities, hypophosphatemia, or hyperphosphaturia. The patient unfortunately did not consent to have a bone biopsy, which would have helped to exclude the diagnosis of hypophosphatemic rickets.

The patient did not have hyperparathyroidism due to hypophosphatemic rickets, because secondary hyperparathyroidism would not have resulted in the frank hypercalcemia seen in this patient.

Pulmonary and endocrine surgery consultants considered the patient inoperable because of end-stage lung disease; thus surgical treatment of the endocrinopathies was not an option. The toxic nodular thyroid disease was treated with iodine I 131 ablation. Bromocriptine therapy was initiated for the hyperprolactinemia, which we presume is due to a prolactinoma. The patient had previously declined estrogen therapy for the hypogonadotropic hypogonadism.

Medical management of the bone disease is particularly problematic in this patient. She refuses estrogen therapy. Furosemide therapy for congestive heart failure puts her at increased risk of dehydration, which could aggravate the hypercalcemia. Calcium therapy likewise could aggravate the hypercalcemia. Oral phosphate therapy is controversial, since it could cause a further increase in parathyroid hormone. It is hoped that correction of the hyperthyroid state will have a significant impact on the hypercalcemia and calciuria, since hyperthyroidism is the only factor in her bone disease that is being corrected. It is unfortunate that these endocrinopathies could not be identified and treated years ago when the patient was a better surgical candidate.

Although one can reasonably approximate the age of onset of only some of this patient's endocrinopathies based on the age of menarche and menopause, one could argue that all of the endocrinopathies were present from childhood and would have been identified earlier had the specific

laboratory testing been available. The classic cutaneous and radiographic lesions of fibrous dysplasia in this patient exclude the possibility that all of her bony abnormalities are due to primary hyperparathyroidism starting in childhood. The question that arises is whether it is important to continue to periodically screen older patients with this syndrome for the advent of new endocrinopathies.

Although there are certainly other potential explanations for the obstetric history in this patient, the history of five miscarriages is of interest. The miscarriages coupled with the fact that both of her offspring are unaffected is in harmony with the Happle hypothesis, which would predict that there is a lethal gene causing the spontaneous loss of all affected offspring.[15]

SUMMARY

In this one patient with McCune-Albright syndrome are seen a multitude of endocrinopathies—more than in any case previously described. Only fibrous dysplasia with café-au-lait spots and/or endocrine hyperfunction are required for the diagnosis of the syndrome. Our patient has polyostotic fibrous dysplasia, café-au-lait spots, and at least four primary endocrinopathies. She had shown precocious puberty (with an ovarian follicular cyst later requiring resection), hyperthyroidism due to toxic nodular thyroid disease, primary hyperparathyroidism, and hyperprolactinemia (with associated hypogonadotropic hypogonadism and premature menopause). With this many organs involved in the same patient, it is hard to imagine that a genetic defect will not soon be identified as the unifying cause of the entire syndrome.

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